

PRELIMINARY AMENDMENT
DIVISIONAL APPLN OF APPLN NO. 07/700,895

Page 63, line 6, delete "40" and insert --39--;
line 10, delete "40" and insert --39--;
line 15, delete "R=Et" and insert --R=Me--;
line 20, delete "40" and insert --39--.

Page 64, line 3, delete "41" and insert --40--.

Page 66, line 16, delete "42" and insert --41--.

Page 71, line 24, after "Ethylenedioxy-" insert
--13,14-dihydro-11R- --.

Page 72, line 2, after "diketo-" insert --11R-dehydroxy- --;
line 5, after "11R-" insert --dehydroxy-11R- --;
line 23, delete "0," and insert --3,--.

Page 78, line 10, delete "52 - 1)" and insert
--52 - 2)--;
line 25, delete "PGE₂" and insert --PGE₂(139)--;
line 26, delete "carbonic" and insert
--carboxylic--.

Page 79, line 20, after "ester" insert --(141)--.

Page 80, line 16, delete "(XXI)" and insert --(XXII)--;
line 20, delete "145" and insert --147--.

Page 81, line 9, delete "PGE_{1a}" and insert --PGE₁--.

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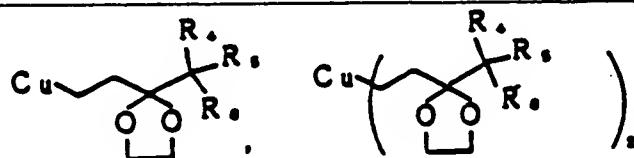
✓ Page 82, line 8, delete "XXII" and insert --XXIII--;
line 10, delete "154" and insert --160--.

✓ Page 85, line 6, after "ester" insert --(141)--.

✓ Page 124, upper right formula, delete "129" and insert
--128--.

Page 8, between lines 7 and 8; please insert --The prosta-
glandin Es of the present invention includes isomers of the
aforementioned compounds. Examples of these isomers include
tautomeric isomer between the hydroxyl group at 11-position and
the carbonyl group of 15-position, i.e. a hemiacetal. Such a
tautomeric isomer is easily formed in a compound having an
electron attractive group such as a fluorine atom.--

Page 13, delete line 1, and insert therefor the following:



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Page 39, lines 1 and 4, delete "3R,S-16R,S" and insert
--3R,S,16R,S--.

Page 77, lines 9-10, 14-15 and 17, delete "diketo-11R-dehydroxy" and insert --diketo-16R,S-fluoro-11R-dehydroxy--.

Page 78, line 8, delete "hydroxymethyl-PGE₂" and insert
--hydroxymethyl-19-methyl-PGE₂--.

Page 78, lines 11, 15 and 19, please delete "hydroxymethyl-PGE₁" and insert --hydroxymethyl-19-methyl-PGE₁--.

Page 79, between lines 15 and 16, please insert - C¹³-n.m.r.
was determined suing a 400 MHz device. The results are as follows:

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No.	PPM	INT(%)	No.	PPM	INT(%)
1	215.845	8.47238	21	77.351	98.89423
2	213.758	8.04458	22	77.030	100.00000
3	210.693	5.10931	23	76.709	94.29728
4	210.460	3.59663	24	72.929	19.24167
5	210.357	3.26243	25	71.294	9.80660
6	178.890	8.35974	26	71.207	8.76754
7	178.700	9.36714	27	65.821	3.16846
8	131.032	18.77798	28	53.999	28.13616
9	130.580	16.85946	29	53.181	18.97531
10	127.135	17.49468	30	47.869	24.43601
11	126.960	20.51506	31	47.051	23.90225
12	97.960	4.23425	32	45.986	12.52490
13	97.799	5.10057	33	45.869	12.09867
14	97.609	3.64508	34	43.753	15.28856
15	97.376	4.06103	35	35.492	16.17178
16	97.171	4.59381	36	33.492	2.97718
17	96.996	8.52154	37	33.230	31.33004
18	96.310	5.02938	38	31.829	16.02193
19	96.208	4.25401	39	31.624	16.87059
20	95.157	8.06931	40	29.858	10.79520

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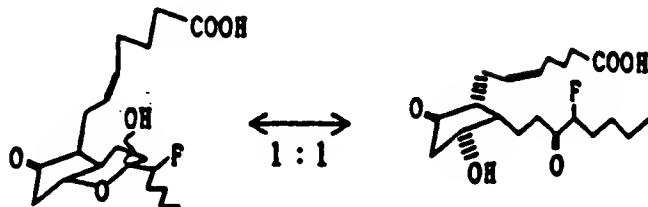
No.	PPM	INT(%)
41	29.712	3.99469
42	29.581	11.04714
43	28.866	7.22944
44	28.647	6.83104
45	28.515	7.46747
46	28.297	6.62025
47	27.786	12.35839
48	27.246	9.17246
49	26.662	28.41152
50	26.458	49.42895
51	24.823	29.72020
52	24.575	3.98072
53	24.458	41.26876
54	23.714	10.46572
55	23.655	11.04843
56	22.415	17.92916
57	22.225	34.46823
58	15.175	3.38720
59	13.906	16.04726
60	13.774	23.45336

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Apparent from the above C¹³-n.m.r. the above compound (140) forms possibly following equilibrium mixture of tautomeric isomers.

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Page 86, after the last line, insert the following:

--Example 60 (see Chart XXVI)

Preparation of 13,14-dihydro-15-keto-16R,S,16R,S-difluoro-PGE₂ (174):

60-1 synthesis of 13,14-dihydro-15R,S-hydroxy-11R-(2-tetrahydropyran-1-yl)oxy-16,16-difluoro-PGE₂ (172):

13,14-dihydro-15R,S-hydroxy-11R-(2-tetrahydropyran-1-yl)oxy-16,16-difluoro-PGE₂ methyl ester (158) (0.731 g) was dissolved in sodium hydroxide:methanol (1:3) solution (60 ml), and stirred at room temperature for 5 hours. The resultant was treated by a usual work-up to give a crude carboxylic acid (172). Yield: 0.722 g.

60-2 synthesis of 13,14-dihydro-15-keto-16,16-difluoro-PGE₂ (174):

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Continued

The title compound (174) was prepared according to the same manner as the process 58-7 in the Example 58 excepting using the compound (172) (0.722 g) instead of the compound (158). Yield: 0.192 g.

The n.m.r. spectrum of the title compound (174) is as follows: ^1H NMR (200 MHz, CDCl_3) δ 0.93 (3H, t, $J=7.1$ Hz), 1.23 -- 2.98 (22H, m), 4.11 -- 4.28 (1H, m, C(11)H), 5.34 -- 5.48 (2H, m).

Mass (m/z) 388 (M^+), 370 ($\text{M}^+-\text{H}_2\text{O}$).

Existence of the hemiacetal is confirmed by ^{13}C n.m.r. spectrum of the compound (174).

After page 130, add the following Synthetic Chart XXVI:

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Synthetic Chart III VI

